Medical Progress

The Clinician's Approach To Drug Interactions

HOWARD F. MORRELLI, M.D., AND KENNETH L. MELMON, M.D., *San Francisco*

■ *Drug interactions are important causes of both unexpected toxic and therapeutic effects. Adverse reactions due to drug interaction are proportional to the number of drugs given and the duration of administration. Although drug interactions may be beneficial, they are most often recognized when they increase mortality or morbidity. The frequency of adverse drug interactions in clinical practice makes it mandatory for physicians to know the drugs and mechanisms involved.*

A drug may potentiate or antagonize the effects of another drug by direct chemical or physical combination, by altering gastrointestinal absorption, by influencing metabolism, transport, or renal clearance, by changing the activity of a drug at its receptor site, or by modifying the patient's response to the drug by a variety of means.

This article stresses the importance of avoiding multiple drug therapy. When such treatment is unavoidable, patients must be carefully observed for evidence of intensified or diminished drug effect. Only this permits the detection and prevention of untoward drug interactions.

IN RECENT YEARS facts have become known that make the common but irrational practice of polypharmacy untenable. Conservative estimates of adverse drug reactions have soared despite the shortcomings of incomplete or biased sampling of patients due to: (1) lack of objective criteria of what actually comprises a reaction, (2) incomplete reporting by physicians and (3) the natural reluctance of physicians or paramedical personnel to attribute an adverse change in a patient's condition to the drugs selected for his treatment.[1] Despite the many factors that lead to underestimation of reaction incidence, it has become unequivocally clear that a major determinant in the development of toxic effects is the number of drugs administered during any period to a patient.[2] Mistakes in administering drugs are encountered when more than a single compound is ordered.[3] Adverse reactions are directly proportional to the number of drugs given and the duration of administration.[4] Since the average in-patient receives six drugs daily,[4] it is no wonder that reaction rates are high.

These reactions are of practical importance: they cause mortality, morbidity, increases in duration of hospital stay and requirements for extra medical attention, patient inconvenience and expense. Their additional importance extends to public health considerations. During a time of

From the Division of Clinical Pharmacology, Departments of Medicine and Pharmacology and Cardiovascular Research Institute, University of California Medical Center, San Francisco.

The work was supported in part by United States Public Health Service Grants HE 09964, HE 06285, GM 01791 and Burroughs Wellcome Clinical Pharmacology Grant.

Reprint requests to: Division of Clinical Pharmacology, University of California Medical Center, San Francisco 94122 (Dr. Morrelli).

overtaxed medical facilities we cannot afford significant iatrogenic contributions to the burdens put upon them.[5]

Potent therapeutic agents cannot be withheld from a patient whose disease may be ameliorated by their use. Unfortunately, potent agents carry with them serious risks, as part of their primary pharmacologic action or as side effects. The rationale of drug choice and the need for multiple drugs must be firmly established on both clinical and pharmacological grounds. When polypharmacy cannot be avoided, an awareness of the frequency and recognition of early reactions is mandatory. Such reactions or interactions may be recognized as a frank adverse effect, or more frequently by the subtle loss or exaggeration of the clinical effect of one of the drugs being given.

This article reviews the known basic mechanisms involved in drug interactions and gives examples of clinical importance. These examples are not intended to be complete, but provide the basis of facts already known. Extension of these principles will provide a valuable means for the detection of additional interactions, and ultimately may be a means of detecting other problems, such as pharmacogenetic anomalies in drug metabolism.[6]

General Considerations

Drug interactions may be clinically helpful, (probenecid extends the half-life of penicillin[7]) or harmful, (phenylbutazone and indomethacin may cause bleeding in patients taking coumarin anticoagulants[8,9]). They may increase (see above), or decrease the half-life of the involved drugs (phenobarbital decreases cortisol[10]). They may augment (insulin and sulfonylureas) or antagonize (thiazide diuretics and sulfonylureas[11]) the desired pharmacologic effect.

The number of drugs involved in interactions is too great to permit memorizing them by trade names. Classification by pharmacologic group and mechanism of interaction is feasible. This approach helps in diagnosing an interaction, in predicting its effects and duration, and in selecting the most logical and effective therapy for the patient.

An interaction may be the result of: (1) a direct physical or chemical combination, (2) altered gastrointestinal absorption, competition for protein binding sites or receptors, (3) increased or decreased metabolism of drug by induction, activation, or inhibition of drug metabolizing microsomal enzymes, (4) alteration of acid-base equilibrium and thereby drug distribution and renal clearance, and (5) alteration of hemodynamics or renal function that influence rates of renal excretion. Examples in each of these categories will be cited and the pharmacologic groups of drugs particularly likely to be associated with drug interactions will be reviewed.

Direct Chemical or Physical Interactions

Direct interactions usually depend on formation of low-energy chemical bonds (hydrogen, ionic and non-covalent). Sometimes the interaction may be useful: The anticoagulant effect of heparin is reversed by binding to protamine. Chelating agents such as ethylenediaminetetracetate have application in selected cases of hypercalcemia or lead poisoning. Chemical interactions may diminish the desired pharmacologic effects of drugs: Tetracyclines are chelating agents, and gastrointestinal absorption of these antibiotics is inhibited when given simultaneously with antacids containing multivalent cations (for example, Ca^{++}, Mg^{++}, or Al^{+++}).[12] Cholestyramine, a drug useful for pruritus in biliary cirrhosis by virtue of its ability to bind bile salts in the gastrointestinal tract, may also bind a variety of drugs within the gastrointestinal lumen, preventing their absorption.[13] Kaolin-containing compounds have been shown to limit the gastrointestinal absorption of the antibiotic lincomycin.[14] Heptobarbital reduces the intestinal absorption of bishydroxycoumarin.[15] Many drugs are incompatible chemically or physically and cannot be used together in intravenous solutions. A recent report lists 104 such drugs, some of which are incompatible with 20 other drugs or vehicles.[16] A handbook of chemistry or a knowledgeable pharmacist should be consulted before therapy with such drugs is begun.

Interactions During Intestinal Absorption

Many factors influence drug absorption from the intestinal tract. Primary phenolic amino acids compete for the same sites for transport. Drugs like alpha-methyl-dopa (an amino acid) might be absorbed slowly when other natural amino acids are ingested in foodstuffs. The state of ionization (determined by the pK), the molecular weight and the polarity of a drug are also factors in absorption. Many drugs are weak acids or weak bases and the proportion of ionized drug is dependent on the pH of its milieu. Un-ionized compounds

TABLE 1.—*Interactions in Transport*

Many drugs are reversibly bound to plasma and tissue proteins, particularly acidic drugs. Only free drug exerts pharmacologic effect. If a very highly bound drug like B is given with a moderately bound drug like A, the bound form of the latter is displaced, enhancing A's effects. See text for qualifications.

	Percent Binding Drug A	*Percent Binding Drug B*
Plasma	1 Free	0.1 Free
	9 Bound	0.9 Bound
Cells	1 Free	0.1 Free
	89 Bound	98.9 Bound

Drugs like A	*Drugs like B*
Pamaquine	Mepacrine
Tolbutamide	Sulphafenazole
Warfarin	Phenylbutazone
Warfarin	Oxyphenbutazone, Sulfinpyrazone
Bilirubin	Salicylates, Sulfonamides
Methotrexate	Salicylates, Sulfonamides
Quinine	Pyrimethamine
Sulfaethylthiadiazole	Phenylbutazone

generally are more soluble in lipid than when they are ionized. In an un-ionized form they readily cross cell membranes. Ionized drugs are generally polar, or water-soluble, and transfer across cell membranes will be relatively slow. For this reason, weak bases are generally more rapidly absorbed than weak acids. However, absorption of weak acids in the small bowel is achieved because of the large surface area.[17] Some drugs, such as iron, are absorbed best when the gastric content is highly acid; other drugs, such as penicillin G, are destroyed at low pH. The package insert of unfamiliar drugs should be consulted as a guide to their administration to ensure optimal absorption.

Interactions at Plasma or Blood Transport Sites

Many drugs are reversibly bound to plasma or tissue proteins (Table 1) and, when bound, they are pharmacologically inert. Displacement of a drug from its binding protein permits it to act, but also facilitates its metabolism or excretion. The net effect of such drug interactions depends on the rate of administration of the second drug, the magnitude and stability of the dose of the first drug, and the relative binding constants of each compound. In practice, chemically induced alterations in the amount of drug bound by protein account for many important toxic reactions. Sulfonylureas such as tolbutamide are bound avidly to protein.[18] When sulfonamides are given in addition to sulfonylureas, the latter will be displaced and hypoglycemia may ensue. Studies have shown a pronounced delay in the plasma disappearance rate of tolbutamide after sulfaphenazole was administered. Diminished hepatic metabolism or renal clearance could be responsible for the prolonged tolbutamide effect, but it is possible that the tolbutamide is displaced from a plasma protein to a tissue protein that releases it more slowly. By such means tolbutamide's disappearance from the body would be delayed. Likewise, phenylbutazone can displace warfarin from its binding protein and induce bleeding. Methotrexate, useful in leukemias, and sometimes used for severe psoriasis, may be displaced by highly acidic, protein-bound drugs such as salicylates and sulfonamides, causing pancytopenia.[19]

An interaction of similar type appears critical in antimalarial therapy. Quinacrine is very highly protein bound. If pamaquine is given simultaneously or shortly after quinacrine therapy, binding sites which biologically will inactivate the pamaquine are not available, and pamaquine toxicity (gastrointestinal, hematopoietic) will be seen.[20] Quinine is not bound as strongly to proteins as pyrimethamine, and when it is given simultaneously in conventional doses severe quinine toxicity (cinchonism, neutropenia) is produced.[21]

Release of endogenous substances from protein-binding sites can occur when acidic compounds are administered. Bilirubin, which is ordinarily bound to plasma proteins,[22] may be released from binding protein and contribute to kernicterus if salicylates and sulfonamides are given during the neonatal period.[23]

Many reports cite alterations in metabolism of one drug by another as the mechanism for prolonged or enhanced drug effect. Unless such reports are documented by appropriate pharmacokinetic studies, interactions in transport cannot be excluded as an underlying or contributing factor.

Interactions at the Receptor Site

Drug effects are determined in part by binding to areas on tissues or cells (receptor sites) (Table 2). The amount of drug which will reach a receptor may be predicted by its affinity constant (the ratio of association to dissociation constants of the receptor and the drug). Knowing that an affinity constant is great does not aid in predicting whether the drug will have primary or direct influence on the tissue (Table 2, Drug B). For example, atropine has a high affinity constant for acetylcholine receptors but possesses no pharmacologic action of its own. Its pharmacologic effect

TABLE 2.—*Interactions at the Receptor Site*

Some drugs, like A in the chart below, combine with receptors to form a complex that elicits a response. The concentration of A, and its affinity (k) for the receptor are determinants of the response. Other drugs, like B, have affinity (K) for the receptor, but the complex elicits no response. If the concentration of B or its affinity constant (K) is higher than A's, no response will be detected. See text for description of interactions.

Drug A + k Receptor ⟶ Drug A-Receptor Complex ⟶ Response

Drug B + K Receptor ⟶ Drug B-Receptor Complex ⟶ No Response

Receptor	*Drugs like A*	*Drugs like B*
Vessel alpha receptor	Norepinephrine	Phentolamine
Bessel beta receptor	Isoproterenol	Propanolol
Cardiac sino-atrial node	Acetylcholine	Atropine
Neuro-muscular junction	Acetylcholine	d-Tubocurarine
Neuro-muscular junction	Succinylcholine	Gallamine
Adrenergic neuron	Norepinephrine	Metaraminol
Adrenergic neuron	Norepinephrine	Guanethidine

depends on its high affinity constant which predicts that it will competitively block receptor binding of acetylcholine which ordinarily elicits a tissue response. Although acetylcholine has intrinsic activity with the receptor, it has a lower affinity constant than atropine, which blocks its tissue effects. This effect can be reversed by adding agents which will allow acetylcholine to accumulate and compete for receptor sites (for example, cholinesterase inhibitors like neostigmine or edrophonium) or by infusing acetylcholine.

Some drugs are distributed to specific tissues and have highly selective effects: D-tubocurarine and gallamine interfere with access of acetylcholine to motor end plates. Anti-sympathetic agents may also work by similar mechanisms: Alpha-stimulating agents like norepinephrine are competitively antagonized by phentolamine or phenoxybenzamine. Beta stimulation by isoproterenol is specifically and competitively antagonized by appropriate doses of propranolol. The adrenergic neurone and its granules can be considered receptors for the storage of norepinephrine—that is, norepinephrine has high affinity but negligible intrinsic activity at this site. An example of interaction which can lead to complex pharmacologic effects is provided by this drug receptor complex. Amphetamines or imiprimines (antidepressants) have been given during antihypertensive therapy with guanethidine. Guanethidine must be taken up by adrenergic neurones before it (1) depletes granular stores of norepinephrine, and (2) prevents physiologic neuronal release of the diminished norepinephrine stores.[24] Amphetamines and imiprimines discharge both guanethidine and norepinephrine from the neurons, resulting in either hypertension (if large amounts of catecholamines are released) or loss of the antihypertensive effect of the guanethidine, if it is no longer allowed access to the receptor.[25]

Knowledge of the mechanism of action of such drugs and their interaction by means of competitive effects on the receptor are the key to proper drug administration and understanding of adverse effects. Understanding interactions at specific receptor sites also leads to the proper choice of effective countermeasures. For example, hypertension which occurs in the example above, or after administration of large doses of guanethidine, could be effectively reversed by alpha blocking agents.

Some interactions require astute and constant observation for their detection. D-tubocurarine and gallamine act by polarizing the motor end plate, and are potentiated by certain antibiotics with similar activity (neomycin, streptomycin, polymyxin[26]) and by drugs that cause potassium depletion, such as the thiazide diuretics.[27] Although the effects of d-tubocurarine and gallamine (polarizing muscle relaxants) can be reversed by cholinesterase inhibitors, this therapy is contraindicated during decamethoniun (depolarizing) paralysis (Table 2).

Interactions by Accelerated Metabolism

Many compounds are metabolized by microsomal enzymes located predominantly in the liver. Enzymatic action usually results in pharmacologic inactivation of the drug but some drugs (dibenzyline, for example) require metabolic activation. Many drugs induce hepatic microsomal activity nonspecifically and thereby increase metabolism of themselves or other agents[28] (Table 3). Phenobarbital and antihistamines are frequently administered in clinical practice and often thought of as relatively innocuous agents. Barbiturates are potent microsomal enzyme inducers and can accelerate the metabolism of antihistamine, cortisone, diphenylhydantoin and other drugs (Table 3). There is definite evidence that bishydroxycoumarin is more rapidly metabolized when given with phenobarbital. As a result, larger than usual amounts of the anticoagulant are required for a therapeutic

TABLE 3.—*Interactions by Altered Hepatic Metabolism of Drugs*

Certain drugs are able to influence the hepatic enzymes that metabolize drugs to inactive products. Those listed below are examples of known or potential clinical importance.

Drugs that are reported to inhibit metabolism of other drugs:

Chloramphenicol: Hexobarbital
para-Aminosalicylic acid: Hexobarbital
Oxyphenylbutazone: Bishydroxycoumarin
Methandrosteneolone: Oxyphenylbutazone
Monamine oxidase inhibitors: Perhaps many

Drugs that induce their own metabolism:

Barbiturates	Phenylbutazone
Glutethimide	Tolbutamide
Meprobamate	Probenecid
Antihistamines	Diphenylhydantoin

Drugs that enhance metabolism of other drugs:

Phenobarbital:	Hexobarbital	Testosterone
	Phenylbutazone	Estradiol-17β
	Diphenylhydantoin	Progesterone
	Griseofulvin	Cortisol
	Bishydroxycoumarin	Androstenedione
Antihistamines:	Pentobarbital	Androstenedione
	Testosterone	Progesterone
Diphenylhydantoin:	Cortisol	

increase in "prothrombin time." If the sedative drug is discontinued, as may happen when a patient is discharged from a hospital, the dose of anticoagulant required to maintain the prothrombin time in the therapeutic range will diminish. Appropriate action must be taken or bleeding will ensue. Many drugs show similar potential.[28,29,30,31,32,33,34] Recognition of other examples of interactions related to altered metabolism will ultimately depend on clinical observations that lead to pharmacokinetic studies which will determine precisely the mechanisms involved in changes in rates of disappearance of a drug.

Interactions by Inhibited Metabolism

A number of drug interactions are based on inhibition of metabolism of one drug by the effects of another. Such effects may be produced by irreversible inhibition of an enzyme responsible for metabolism of the first drug or by competing as a substrate for the same enzyme. The xanthine oxidase inhibitor, allopurinol, prolongs the half-life and increases the effects of 6-mercaptopurine by inhibiting the enzyme responsible for the latter's metabolism.[35] The cancer chemotherapeutic agent must be given in less than usual doses to prevent serious toxicity.[36] Other possible examples of the same phenomena include potentiation of the hypoglycemic effects of tolbutamide and the toxic effects of diphenylhydantoin by Dicumarol®.[37,38] In turn, tolbutamide extends the half-life of a similar chemical, sulfonamide. Such potentiation probably is produced by competition of the drugs for metabolizing enzymes. Potentiation occurs when sufficient amounts of drug are given to produce saturation of the affected enzymes.

Some drugs have complex mechanisms for potentiation of a second compound. Although it is true that monamine oxidase inhibitors (MAOI for example, pargyline and tranylcyromine) may potentiate the effects of tyramine by prolonging its half-life, inhibition of the oxidation of tyramine accounts for only part of the MAOI potentiation of tyramine's effect. During MAO inhibition, tissue stores of catecholamines increase. A significant contribution to the potentiated effect of tyramine and other catecholamine-releasing agents is the expanded catecholamine pool available for pharmacologic release, in addition to actual prolongation of the catechole releasing agent's half-life.[39]

Altered metabolism may be solely responsible for potentiation of the action of sedatives, narcotics, anesthetics, antiparkinsons, antihypertensive agents, tricyclic antidepressants, insulin and oral hypoglycemic agents by MAOI, but care is required to assess the potential contribution of alteration in protein binding, renal clearance, or tissue responsiveness when one drug potentiates another.[40] Likewise, potentiation of similar classes of drugs by hydrazine derivatives such as isoniazid and the antineoplastic agent procarbazine, may be related to their MAOI.

Influence of Acid-Base Balance on Drug Action

One determinant of the concentration of a drug at its receptor site is related to pH, which affects drug distribution. The diffusion of lipid-soluble weak acids and bases depends upon their state of ionization. Ionized drugs diffuse poorly across cell membranes. Intracellular sites are normally more acidic than plasma; hence weak bases attain higher intracellular concentrations than weak acids. During pathologic processes, or as a result of therapeutic interventions, plasma pH may be altered, with consequent changes in the concentration of drugs at receptor sites. For example, plasma phenobarbital (site of action intracellular) falls with respiratory acidosis and coma deepens as the drug enters cells; the reverse obtains with ventilation or bicarbonate therapy.[41] Mecamylamine is a weak base with an extracellular site of action;

APPENDIX A

A SUMMARY OF SELECTED AND POTENTIAL (ANIMAL EXPERIMENTS) DRUG INTERACTIONS

When the Patient Takes this Drug	*And this Drug Is Added*	*These Symptoms or Findings Might Result*
ANALGESICS		
Aspirin	Anticoagulant	Bleeding
	Para-aminosalicylic acid	Salicylism
	Probenecid	Decreased uricosuric effect of Probenecid
Meperidine	MAO inhibitor	Enhanced sedation, possible cardiovascular changes
	Phenothiazine	Enhanced sedation, respiratory depression
Phenylbutazone	Coumarin anticoagulant	Chronic: Decreased anticoagulant effect
	Sulfonylurea (oral hypoglycemic)	Hypoglycemia
Phenyramidol (Muscle relaxant)	Bishydroxycoumarin	Bleeding
	Diphenylhydantoin	Diphenylhydantoin toxicity (cerebellar signs)
ANTIBIOTICS		
Chloramphenicol	Penicillin	Decreased penicillin effect
	Barbiturate	Enhanced barbiturate effect
	Codeine	Enhanced codeine effect
Griseofulvin	Anticoagulant	Decreased anticoagulant effect
	Phenobarbital	Decreased griseofulvin effect
Penicillin G	Chloramphenicol	Decreased penicillin effect
	Tetracycline	Decreased penicillin effect
Neomycin, Kanamycin, Streptomycin	Curare	Increased curare effect
Lincomycin	Kaolin	Diminished lincomycin effect
Para-aminosalicylic acid	Barbiturate	Enhanced barbiturate effect
Sulfonamide	Anticoagulant	Increased anticoagulant effect
	Sulfonylurea	Hypoglycemia
Tetracycline	Antacid with divalent cations	Diminished tetracycline effect
	Methicillin	Incompatible in I.V. solution
	Chloramphenicol	Incompatible in I.V. solution
ANTIMALARIALS		
Mepacrine	Pamaquine	Pamaquine toxicity, methemoglobinemia neutropenia
Pyrimethamine	Quinine	Quinine toxicity, cinchonism, neutropenia
COUMARIN ANTICOAGULANTS		
(e.g. Bishydroxycoumarin, Warfarin, etc.)	Antihyperlipemic agents	Increased anticoagulant effect
	Glutethimide	Decreased anticoagulant effect
	Chloral hydrate	Decreased anticoagulant effect
	Chlordiazepoxide	Decreased anticoagulant effect
	Diazepam	Decreased anticoagulant effect
	Griseofulvin	Anticoagulant resistance
	Meprobamate	Anticoagulant resistance
	Norethandrolone	Increased anticoagulant sensitivity
	Oxyphenbutazone	Increased anticoagulant sensitivity
	Phenobarbital	Decreased anticoagulant effect
	Phenylbutazone	Increased anticoagulant sensivity: Acute
	Phenylbutazone	Decreased anticoagulant sensitivity: Chronic
	Propylthiouracil	Increased anticoagulant effect
	Phenyramidol	Increased anticoagulant sensitivity
	Quinidine	Enhanced warfarin effect
	Salicylate	Increased anticoagulant sensitivity
	Sulfonamide	Increased anticoagulant sensitivity
	Long acting sulfonamides	High sulfonamide blood levels
	Tolbutamide	Hypoglycemia
Heparin	Polymyxin B	Incompatible in I.V. solution
ANTIDEPRESSANTS		
MAO Inhibitors:		
Isocarboxazid	Alcohol	Exaggerated alcohol effect
Phenelzine	Amphetamine	Agitation hypertensive crisis
Tranylcypromine	Anesthetic (general)	Enhanced central nervous system depression
Isonicotinic acid hydrazide		
Pargyline	Anti-Parkinsonism agent	Increased anti-parkinsonism agent
(Other Hydrazine derivatives potentially)		Atropine-like poisoning
	Barbiturate	Enhanced sedation
	Choral hydrate	Enhanced sedation
	Cocaine	Hypertension
	Food or alcoholic beverage containing tytramine	Hypertensive crisis
	Insulin	Hypoglycemia
	Meperidine	Hypertension or hypotension, enhanced central nervous system, effects depressed respiration
	Methyldopa	Excitation, hypertension
	Chlordiazepoxide, diazepam	Enhanced sedation
	Imipramine	Atropinism: excitation, coma, tremor, sweating, fever, delerium, seizures, rigid
	Phenothiazine	Extrapyramidal reaction, hypertension
	Reserpine	Excitation
	Sympathomimetic	Hypertensive crisis
	Thiazide diuretic	Hypothension
	MAO inhibitors	Agitation, tremor, opisthotonos coma, fever
Tricyclic antidepressants:		
Amitriptyline	Guanethidine	Hypertension, loss of antihypertensive action
Desipramine	Benzodiazepines	Atropinism
Impramine	MAO inhibitors	Severe atropine-like toxicity
Nortriptyline		Atropinism, hypotension

When the Patient Takes this Drug	*And this Drug Is Added*	*These Symptoms or Findings Might Result*
ANTIHYPERTENSIVES		
Guanethidine	Amphetamine	Hypertension
	Anesthetic	Hypotension
	Levarterenol	Increased response
	Mephentermine	Decreased response
	Metaraminol	Decreased response
	Phenothiazine	Hypotension
	Tricyclic antidepressant	Hypertension or loss of antihypertensive effect
Mecamylamine	Sympathomimetic	Sympathomimetic sensitivity
	Thiazide diuretic	Increased antihypertensive effect
Methyldopa	Anesthetic	Hypotension
	Levarterenol	Increased response to Levarterenol
	MAO inhibitor	Hypertension
	Sympathomimetic	Direct acting: Increased sensitivity Norepinephrine liberators: decreased effect
	Anesthetic	Increased anesthetic effect
Reserpine	Digitalis	Bradycardia
	Anesthetic	Hypotension
	Levarterenol	Increased Levarterenol effect
	MAO inhibitor	Excitation, blood pressure increase
	Metaraminol	Pressor response (Decreased)
	Phenothiazine	Hypotension
	a sympathomimetic (direct acting)	Increased response
ANTINEOPLASTIC AGENTS		
6-mercaptopurine	Allopurinol	Pancytopenia
Methotrexate	Aspirin	Pancytopenia
	Sulfonamide	Pancytopenia
Procarbazine	(See MAO inhibitor)	(See MAO inhibitor)
BARBITURATES		
Phenobarbital	Alcohol	Increased alcohol effect
	Anticoagulant	Decreased anticoagulant effect
	Antihistamine	Decreased antihistamine effect Additive sedative effect
	Phenylbutazone	Decreased phenylbutazone effect
	Diphenylhydantoin	Decreased Dilantin effect
	Griseofulvin	Decreased griseofulvin effect
	MAO inhibitor	Increased phenobarbital effect
	Benzodiazepines	Enhanced sedation
	Phenothiazine	Enhanced sedation
	Steroid (Cortisol, androgen, estrodiol 17β, progesterone)	Decreased steroid effect
DIGITALIS		
Digitalis	Calcium	Digitalis toxicity
	Thiazide diuretic	Digitalis toxicity
	Reserpine	Bradycardia
	Thyroxine	Decreased digitalis effect
DIURETICS		
Thiazine diuretics	Digitalis	Digitalis toxicity
	Hydralazine	Hypotension
	MAO inhibitor	Hypotension
	Mecamylamine	Hypotension
	Sulfonylurea	Aggravated glucose intolerance
ORAL HYPOGLYCEMICS		
Sulfonylureas	Coumarin anticoagulant	Hypoglycemia
	Phenylbutazone	Hypoglycemia
	Sulfonamide	Hypoglycemia
	Thiazide diuretic	Aggravated glucose intolerance
SEDATIVES & TRANQUILIZERS (See also barbiturates)		
Chloral hydrate	Coumarin anticoagulant	Decreased anticoagulant effect
	MAO inhibitor	Enhanced sedation
Glutethimide	Coumarin anticoagulant	Decreased anticoagulant effect
Benzodiazepines	Alcohol	Enhanced sedation
	Barbiturate	Enhanced sedation
	MAO inhibitor	Enhanced sedation
	Phenothiazine	Enhanced sedation
	Tricyclic Antidepressant	Enhanced sedation, atropinism
Phenothiazines	Alcohol	Enhanced sedation
	Antihistamine	Sedation, atropinism
	Antihypertensive	Increased hypotension (especially postural)
	Barbiturate	Enhanced sedation
	MAO inhibitor	Extrapyraminal reactions, hypertension
	Meperidine	Enhanced sedation, respiratory depression
	Morphine	Enhanced sedation, analgesia
	Reserpine	Hypotension
	Thiazide diuretic	Hypotension
	Tricyclic Antidepressant	Hypotension, atropinism, seizures
STEROIDS		
Estrogen/ progesterone	Phenobarbital	Decreased estrogen/progesterone (in animals)
Hydrocortisone	Antihistamine	Decreased hydrocortisone effect
	Barbiturate	Decreased hydrocortisone effect
	Diphenylhydantoin	Decreased hydrocortisone effect
Norethandrolone	Anticoagulant	Increased anticoagulant effect
Methandrostenolone	Oxyphenbutazone	Increased oxyphenbutazone effect
ANTIHISTAMINES		
	Alcohol	Central nervous system depression
	Sedatives	Central nervous system depression
	Steroid (androgens, progesterone)	Decreased steroid effect
	MAO inhibitor	Increased antihistamine sedation, atropinism
	Parasympatholytics	Increased parasympatholytic effect, atropinism
	Phenothiazine	Additive effect sedation, atropinism
	Reserpine	Sedation, atropinism

TABLE 4.—*Influence of pH on Drug Absorption, Distribution, and Excretion*

The diffusion of lipid soluble weak acids and bases depends in part upon their state of ionization in a given milieu. Ionized drugs diffuse across lipid rich cell membranes poorly. Intracellular sites are more acidic than plasma, hence alkaline drugs accumulate in cells. Other factors such as extensive protein binding, degree of lipid solubility, and partition coefficient may alter the predicted effect based upon pH of the drug alone.

Process	*Drug A (Weak Acid)*	*Drug B (Weak Base)*
Gastric absorption	Relatively rapid	Relatively slow
Small bowel absorption	Relatively slow	Relatively rapid
Plasma/Cell Ratio	Low	High
Renal clearance in:		
Acid Urine	Low	High
Alkaline Urine	High	Low
Examples:	Sulfonamides	Antihistamines
	Salicylic Acid	Mecamylamine
	Phenobarbital	Amphetamine

acidosis increases its plasma levels and may cause hypotension.[42] Table 4 represents some commonly used drugs which are weak acid and bases.

Drug Interactions by Altered Renal Clearance

As pH may affect cellular distribution of a drug, so may urinary hydrogen ion concentration influence clearance of drugs by the kidney. Changes in urinary pH induced by disease—or as a result of therapy with ammonium chloride, sodium bicarbonate, thiazides or acetazolamide—may profoundly influence the renal excretion of many drugs that are weak acids or bases. Ionized drugs diffuse slowly across cell membranes and are slowly reabsorbed from the glomerular filtrate by the tubules; hence they are cleared relatively rapidly. Weak acids are reabsorbed poorly from an alkaline urine and weak bases are reabsorbed poorly from an acidic urine. Accordingly, weak acids such as phenobarbital and salicylic acid are rapidly cleared by the kidney during alkaline diuresis, while basic drugs such as amphetamine or mecamylamine would be cleared relatively slowly.[43]

An interaction in the kidney may only be partially accounted for by alteration in renal clearance of the drug. For instance, salicylates may interfere with the uriosuric effects of probenecid by antagonistic action on the tubular sites of uric acid clearance but not by actually altering clearance of either drug. Likewise the ability of probenecid to delay the excretion of penicillin is due to a direct tubular effect of the former. Once again data must be carefully analyzed before interactions can be attributed solely to their competing renal effects. When hypoglycemia occurred after phenylbutazone was added to a regimen using acetohexamide, clearance of the active metabolite hydroxyhexamide appeared diminished.[44] However, studies are needed to document this as the sole factor contributing to the hypoglycemia.

Interactions with the Psychotherapeutic Drugs

The phenothiazines are extremely useful in psychiatric disorders when patients require tranquilization. However, the effects they have on the central nervous system may predispose to potentiation of barbiturates, alcohol and narcotics. Complex changes in cardiovascular function are observed during administration of phenothiazines. Their central and peripheral effects may lead to postural hypotension. Because phenothiazines can block alpha receptors, the choice of drugs for the treatment of hypotension is limited. If the pressor used elicits both alpha and beta responses, the net effect during alpha receptor blockade could be beta mediated arterial dilation and, paradoxically, exaggerated hypotension.[45] If used with monamine oxidase inhibitors, phenothiazines may produce severe extrapyramidal reactions and hypertension.[46]

Phenothiazines lower the seizure threshold, and when possible should be avoided in epileptic patients. This advice is particularly pertinent when the patients are taking other agents like the tricyclic antidepressants that also lower the seizure threshold. Phenothiazines have a quinidine-like action on myocardial conducting and pacemaking tissues. Ventricular tachycardia has been reported during phenothiazine therapy.[47] Treatment of such an arrhythmia should be similar to that used for quinidine toxicity, namely, induction of alkalosis, and/or use of isoproterenol, or electrical methods.[48] Use of cardiac depressant drugs like quinidine should be avoided.

The tricyclic antidepressants have largely supplanted the monamine oxidase inhibitors for treatment of depression. When they are given simultaneously with or shortly following administration of monamine oxidase inhibitors, severe atropine-like reactions may occur. Similar reactions may occur when the benzodiazepines are given with phenothiazines.[49] The benzodiazepines are relatively safe agents taken alone, but they potentiate the sedative and/or atropine-like effects of alcohol, barbiturates, phenothiazines and the tricyclic antidepressants. Monamine oxidase inhibitors also

TABLE 5.—*Oral Anticoagulant Interactions*

Drug	*Putative Mechanism*
DIMINISHED Anticoagulant Effect:	
Cholestyramine	Direct chemical
Vitamin K	Direct biochemical
Barbiturates	Decreased G-1 absorption
Barbiturates	Enhanced metabolism
Glutethimide	Enhanced metabolism
Griseofulvin	Enhanced metabolism
Meprobamate	Enhanced metabolism
Diphenylhydantoin	Enhanced metabolism
Chloral Hydrate	Enhanced metabolism
Phenylbutazone (late)	Enhanced metabolism
Diazepam	Enhanced metabolism
Chlorpromazine	Enhanced metabolism
? Antihistamines	
? Chlordane, DDT	
ENHANCED Anticoagulant Effect:	
Aspirin	Direct biochemical
Propylthiouracil	Direct biochemical
Quinidine	Direct biochemical
Phenylbutazone (early)	Protein binding
Antibiotics	Decreased G-1 flora
Oxyphenbutazone	Decreased metabolism
Phenyramidol	?
Dextrothyroxine	?
Levothyroxine	?
Clofibrate	?
Androsterone	?
OTHER DRUG Enhanced:	
Tolbutamide: Dicumarol	Protein binding
Dilantin: Dicumarol	?
Long acting Sulfas: Dicumarol	?

enhance the sedative effects of benzodiazepines.[50]

Interactions of the psychotherapeutic agents with drugs of other categories has been recognized. Both phenothiazines[51] and benzodiazepines alter the effects of oral anticoagulants.

Drug Interactions Conditioned by Previous Drug Effects or Disease

In some patients, drug toxicity is not produced by simple additive effects of drugs given simultaneously. Toxicity appears as a result of drug-induced changes in the patient. For example, thiazide diuretics, by producing potassium loss may predispose patients to digitalis toxicity. Likewise, reserpine, which depletes myocardial stores of norepinephrine, may cause undue bradycardia when digitalis is given.[52] Catecholamine depleting agents like guanethidine and reserpine may render patients refractory to pressor agents that depend upon catecholamine release for their activity (mephentermine and metaraminol). Reserpine may also prevent uptake of administered catecholes into storage sites and thus may render patients hypersensitive to infused norepinephrine.[53] Propanolol inhibits beta sympathetic responses and has been blamed for lack of sympathetic response to hypoglycemia caused by insulin or sulfonylureas.[54]

Spontaneous variability of response to therapy during disease states can alter the relationship between simultaneously administered drugs. During hormonal replacement in patients with hypothyroidism, the dose of barbiturate sedatives and digitalis required to maintain a stable effect increases.[55] Conversely, thyroid replacement would promote a faster turnover of clotting factors and decrease the dose requirements of anticoagulant drugs.[56] Although the mechanism is not fully defined, administration of the antihyperlipemic drugs results in diminished requirements for oral anticoagulant drugs.[57] Antibiotic therapy which alters intestinal flora that normally synthesize vitamin K, reduces the prothombinopenic dose of warfarin. Certain antibiotic combinations, especially those involving the combination of a bacteriostatic with a bacteriocidal agent may be antagonistic. In most clinical settings the combinations can be avoided.[58] Spironolactone antagonizes the effects of aldosterone, and may result in hyperkalemia if potassium salts are given. This effect persists for several days after spironolactone is discontinued, as the initial onset of action of aldosterone is slow.

Conclusion

This review has emphasized the importance of drug interactions that can occur during administration of commonly used drugs. Other reviews are more complete.[59,60,61] The recognized drug interactions for a single category of drugs, the oral anticoagulants, is given in Table 5. The list is long, and will undoubtedly lengthen. The current rate of publications in the drug interaction field is awesome. Two of the publications helpful in keeping current in this area are: *Clin-Alert* (published by Science Editors, Inc., P.O. Box 1174, Louisville, Kentucky 40202) and the Food and Drug Administration *Clinical Experience Abstracts* (D.H.E.W. Food and Drug Administration Bureau of Medicine, Medical Literature Branch, Washington, D.C. 20204) which summarize both individual drug reactions and drug interactions as they appear in the literature. Another library reference of use is Adverse Reaction Titles, Excerpta Medica Foundation, New York Academy of Medicine Building, 2 East 103rd Street, New York, N.Y. 10029.

The practitioner can avoid or detect interactions by continuing to be aware of their possibility, by avoiding multiple drug therapy when possible, and by carefully monitoring drug effects in his patients.

If evidence of enhanced or diminished drug activity is seen when a new drug is added to a therapeutic regimen, an interaction should be suspected until ruled out.

The number of drugs involved in interactions and their complex interplay with disease states will eventually require computer methods to store information about known interactions, and to prospectively predict potential drug interactions based upon information regarding the chemical and pharmacologic properties of the agents used in patients with given disorders. Awaiting this innovation, the physician must protect his patients by prudence in drug choice, and perspicacity during multiple drug therapy.

Appendix A is a summary of selected and potential (animal studies) drug interactions. Appendix B is a list of the generic and trade names of drugs mentioned in this review.

APPENDIX B

Generic and Trade Names of Drugs

ANALGESICS:

Aspirin (Salicylates) ..... *Aspirin®*
Meperidine ..... *Demerol®*
Phenylbutazone ..... *Butazolidin®*
Oxyphenbutazone ..... *Tandearil®*

MUSCLE RELAXANTS:

Phenyramidol ..... *Analexin®*

ANTIBIOTICS:

p-Aminosalicylic acid ..... *PAS®*
Chloramphenicol ..... *Chloromycetin®*
Griseofulvin ..... *Fulvicin®, Grifulvin®, Grisactin®*
Penicillin ..... *Abbocillin®, Pentids®, Sugracillin®*, etc.
Sulfonamides ..... *Acusul®, Gantanol®*, etc.
Long acting sulfonamide ..... *Madribon®*
Lincomycin ..... *Lincocin®*
Sulfaphenazole ..... *Sulfabid®*
Tetracycline ..... *Achromycin®, Panmycin®, Sumycin®*, etc.
Streptomycin ..... *Streptomycin®*
Neomycin ..... *Mycifradin®*
Polymyxin ..... *Aerosporin®*
Isoniazid ..... *Niconyl®, Nicozide®, Nydrazid®*
Methicillin ..... *Staphcillin®*
Sulfaethylthiadiazole ..... *Sul-Spantab®*

ANTICOAGULANTS:

Coumarins:
- Bishydroxycoumarin ..... *Dicumarol®*
- Ethyl biscoumacetate ..... *Tromexan® ethylacetate*
- Warfarin ... *Coumadin®, Panwarfin®, Prothromadin®*
- Phenprocoumon ..... *Marcoumar®, Liquamar®*
- Acenocoumarin ..... *Nicoumalone®, Sintrom®*
- Cyclocoumarol ... *Cumopyran®, Link Compound 63, Methopyranorin®*

Heparin ..... *Panheprin® (sodium heparin)*
Protamine Sulfate ..... *Protamine sulfate®*

ANTICONVULSANTS:

Diphenylhydantoin ..... *Dilantin®*

ANTIDEPRESSANTS:

Monamine Oxidase Inhibitors:
- Pargyline ..... *Eutonyl®*
- Tranylcypromine ..... *Parnate®*

Amphetamines:
- Amphetamine ..... *Benzedrine®*
- Methamphetamine ..... *Desoxyephedrine®, Desoxyn®, Methidrine®*

Tricyclic antidepressants:
- Imipramine ..... *Tofranil®*
- Nortriptyline ..... *Aventyl®*
- Amytriptyline ..... *Elavil®*
- Desmethylimipramine ..... *Norpramin®*

ANTIHYPERTENSIVES:

Guanethidine ..... *Ismelin®*
Alpha-methyldopa ..... *Aldomet®*
Mecamylamine ..... *Inversine®*
Hydralazine ..... *Apresoline®*
Reserpine ..... *Rauloydin®, Reserpoid®, Rau-sed®*, etc.

ADRENERGIC BLOCKING AGENTS:

Alpha:
- Phentolamine ..... *Regitine®*
- Phenoxybenzamine ..... *Dibenzyline®*

Beta:
- Propranolol ..... *Inderal®*

PRESSOR AGENTS:

Direct acting:
- Alpha stimulating, norepinephrine *Levophed®*
- Beta stimulating, isoproterenol ..... *Isuprel®*

Indirect acting:
- Metaraminol ..... *Aramine®*
- Mephentermine ..... *Wyamine®*

NEUROMUSCULAR BLOCKING AGENTS:

Decamethonium ..... *C10®, Syncurine®*
D-tubocurarine ..... *Tubarine®, Tubadil®*
Gallamine ..... *Flaxedil®*
Succinylcholine chloride ..... *Diacetylcholine® chloride, Anectine®, Suxamethonium®*, etc.

PARASYMPATHETIC AGENTS:

Edrophonium ..... *Tensilon®*
Neostigmine ..... *Prostigmine® bromide*
Atropine ..... *Atropine®*

ANTINEOPLASTIC AGENTS:

6-Mercaptopurine ..... *Purinethol®*
Methotrexate ..... *Amethopterin®*
Procarbazine ..... *Natulan®*

ANTIMALARIALS:

Quinacrine ..... *Mepacrine®, Atabrine®, Atebrin®*
Pamaquine ..... *Aminoquin®, Deprochin®, Plasmaquin®*
Quinine ..... *Quinamm®*
Pyrimethamine ..... *Daraprim®*

SEDATIVES:

Phenobarbital ..... *Luminal®, Talpheno®*
Chloral hydrate ..... *Noctec®, Dormal®, etc.*
Gluthethamide ..... *Doriden®*
Meprobamate ..... *Equanil®, Miltown®*

BENZODIAZEPINES:

Chlordiazepoxide ..... *Librium®*
Diazepam ..... *Valium®*
Oxazepam ..... *Serax®*

PHENOTHIAZINES:

Chlorpromazine ... *Thorazine®, Largactil®, Megaphen®*
Promazine ..... *Sparine®*
Triflupromazine ..... *Vesprin®*
Fluphenazine ..... *Permitil®, Proxlixin®*
Prochlorperazine ..... *Campazine®*
Trifluoperazine ..... *Stelazine®*
Thioridazine ..... *Mellaril®*

ANTIHYPERLIPEMIC DRUGS:

D-thyroxine ..... *Choloxin®*
Clofibrate ..... *Atromid-S®*
Androsterone ..... *Atromid®*

DIURETIC AGENTS:

Spironolactone ..... *Aldactone®*
Acetazolamide ..... *Diamox®*
Benzothiadiazides: (Thiazides)
Chlorothiazide ..... *Diuril®*
Hydrochlorothiazide .. *Oretic®, Hydrodiuril®, Esidrix®*
Flumethazide ..... *Ademol®*
Hydroflumethazide ..... *Saluron®*
Bendroflumethazide ..... *Naturetin®*
Benzthiazide ..... *Naclex®, Exna®*
Trichlormethiazide ..... *Naqua®, Metahydrin®*
Methyclothiazide ..... *Enduron®*
Polythiazide ..... *Renese®*
Cyclopenthiazide ..... *Navidrex®*
Cyclothiazide ..... *Anhydron®*

HYPOGLYCEMIC AGENTS:

Sulfonylureas:
Tolbutamide ..... *Orinase®*
Chlorpropamide ..... *Diabinese®*
Tolazamide ..... *Tolinase®*
Insulin

HORMONES:

Cortisol ..... *Cortisol®, Cortef®, Hydrocortisone®, Solucortef®*, etc.
Norethandrolone ..... *Nilevar®*
Progesterone ..... *Progesterone®*
Estrogens ..... *Esteed®, Estinyl®*, etc.
Thyroid .. *Armour® thyroid, Cytomel®, Synthroid®*, etc.

OTHER:

Digitalis ..... *Crystodigin®, Digoxin®, Purodigin®*, etc.
Quinidine ..... *Quinidex®, Quinora®*, etc.
Cholestyramine ..... *Cuemid®*
Kaolin ..... *Kaopectate®*, etc.
Probenecid ..... *Benemid®*
Allopurinol ..... *Zyloprim®*
Ethylenediaminetetracetate ..... *EDTA®, Versene®, Edathamil®*
Sulfinpyrazone ..... *Anturane®*

ANTIHISTAMINES:

Ethylenediamines:
Antazoline ..... *Antistine®*
Chloromethapyrilene citrate N.F. ..... *Chlorothen®, Tagathen®*
Clemizole HC1 N.N.D. ..... *Allecur®, Reactrol*
Methaphenilene HC1 ..... *Diatrine®*
Methapyrilene HC1 N.F. ..... *Histadyl®, Thenylene®, Semikon®*
Pyrilamine maleate (mepyramine, pyranisamine) U.S.P. ... *Neo-Antergen®, Paramal®, Stangen®, Thylogen®*
Thenyldiamine HC1 N.F. ..... *Thenfadil®*
Thonzylamine HC1 N.F. ... *Anahist®, Neohetramine®*
Tripelennamine HC1 U.S.P. ..... *Pyribenzamine®*

Amino Alkyl Ethers:
Bromodiphenhydramine HC1 ..... *Ambodryl®, Bromo-Benadryl®*
Carbinoxamine maleate N.F. ..... *Clistin® (d-isomer, Twiston®)*
Diphenhydramine HC1 U.S.P. ..... *Benadryl®*
Diphenylpyraline HC1 N.N.D. .... *Diafen®, Hispril®*
Doxylamine succinate U.S.P. ..... *Decapryn®*

Alkylamines:
Brompheniramine maleate N.F. ..... *Dimetane® (d-isomer, Disomer, N.N.D.)*
Chlorpheniramine maleate U.S.P. ... *Chlortrimeton® (d-isomer Polaramine®, N.N.D.)*
Dimethindene maleate N.N.D. ..... *Forhistal®*
Pheniramine maleate N.F. ..... *Trimeton®*
Pyrrobutamine phosphate N.N.D. ..... *Pyronil®*
Triprolidine HC1 N.N.D. ..... *Actidil®*

Piperazines:
Buclizine HC1 ..... *Softran®*
Cyclizine HC1 U.S.P. ..... *Marezine®*
Chlorcyclizine HC1 U.S.P. .... *Di-Paralene®, Perazil®*
Meclizine HC1 U.S.P. ..... *Bonine®*

REFERENCES

1. Lasagna, L.: Drug toxicity in man: The problem and the challenge, Ann. N.Y. Acad. Sci., 123:312-315, 12 Mar. 1965.
2. Vere, D. W.: Errors of complex prescribing, Lancet, 1:370-373, 13 Feb. 1965.
3. Simmons, M., Parker, J. M., Gowdy, C. W., and Coulter, W. K.: Adverse drug reactions during hospitalizations, Canad. Med. Assn. J., 98:175, 20 Jan. 1966.
4. Smith, J. W., Seidl, L. G., and Cluff, L. E.: Studies on the epidemiology of adverse drug reactions. V. Clinical factors influencing susceptibility, Ann. Intern. Med., 65:629-640, Oct. 1966.
5. Modell, W.: Hazards of new drugs, Science, 139:1180-1185, 22 Mar. 1963.
6. Motulsky, A. G.: The genetics of abnormal drug responses, Ann. N.Y. Acad. Sci., 123:167-177, 12 Mar. 1965.
7. Weiner, I. M., Washington, J. A., II, and Mudge, G. H.: On the mechanism of action of probenecid on renal tubular secretion, Bull. Johns Hopkins Hosp., 106:33-46, June 1960.
8. Aggeler, P. M., O'Reilly, R. A., Leong, L., and Kowitz, P. E.: Potentiation on anticoagulant effect of warfarin by phenylbutazone, New Eng. J. Med., 276:496-501, 2 Mar. 1967.
9. Hoffbrand, B. I., and Kininmonth, D. A.: Potentiation of anticoagulants, Brit. Med. J., 2:838-839, 24 June 1967.
10. Conney, A. H., Jacobson, M., and Schneidman, K.: Induction of liver microsomal cortisol 6*B*-hydroxylase by diphenylhydantoin or phenobarbital: An explanation for the increased excretion of 6-hydroxycortisol in humans treated with these drugs, Life Sci., 4:1091-1098, May 1965.
11. Dollery, C. T., Pentecost, B. L. and Samaan, N. A.: Drug induced diabetes, Lancet, 2:735-737, 13 Oct. 1962.
12. Dearborn, E. H., Litchfield, J. T., Jr., Eisner, H. J., Corbett, J. J. and Dunnett, C. W.: The effect of various substances on the absorption of tetracycline in rats, Antibiot. Med. Clin. Ther., 4:627, Oct. 1957.
13. Council on Drugs: An antipruritic agent for primary biliary cirrhosis and cholestatic jaundice. Cholestyramine resin (Cuemid), JAMA, 197:261-262, 25 July 1966.
14. Wagner, J. G.: Biopharmaceutics: Absorption aspects, J. Pharm. Sci., 50:539-587, May 1961.
15. Aggeler, P. M., and O'Reilly, R. A.: The pharmacological basis of oral anticoagulant therapy, Thromb. Diath. Haemorrh. Suppl., 21:227-256, 1966.
16. Pelissier, N. A., and Burgee, S. L., Jr.: Guide to incompatibilities, Hosp. Pharm., 3:15-32, Jan. 1968 (104 incompatible drugs cited, some of these being incompatible with as many as 20 other drugs).
17. Hogben, C. A. M., Tocco, D. J., Brodie, B. B., and Schanker, L. S.: On the mechanism of intestinal absorption of drugs, J. Pharmacol. Exp. Ther., 125:275-282, April 1959.
18. Wishinsky, H., Glasser, E. J., and Perkal, S.: Protein interactions of sulfonyurea compounds, Diabetes, 11, Suppl., 18-25, 1962.
19. Dixon, R. L., Henderson, E. S., and Rall, D. P.: Plasma protein binding of methotrexate and its displacement by various drugs., Fed. Proc., 24:454, Mar.-Apr. 1965.
20. Zubrod, C. G., Kennedy, T. J., and Shannon, J. A.: Studies on the chemotherapy of human malarias. VIII. The physiological disposition of pamaquine, J. Clin. Invest., 27:114-120, May 1948.
21. Blount, R. E.: Management of chloroquin-resistant falciparum malaria (personal communication addendum), Arch. Int. Med., 119:557-560, June 1967.
22. O'Dell, G. B.: Studies in Kernicterus. I. The protein binding of bilirubin, J. Clin. Invest., 38:823-833, May 1959.
23. Silverman, W. A., Andersen, D. H., Blane, W. A., and Crozier, D. N.: A difference in mortality rate and incidence of kernicterus among premature infants allotted to two prophylactic antibacterial regimens, Pediatrics, 18:614-625, 1956.
24. Oates, J.: Personal communication.
25. Leishman, A. W. D., Mathews, H. L., and Smith, A. J.: Antagonism of guanethidine by imipramine, Lancet, 1:112, 12 Jan. 1963.
26. Vital Brazil, O., and Corrado, A. P.: The curariform action of streptomycin, J. Pharmacol. Exp. Ther., 120:452-459, Aug. 1957.
27. Koelle, G. B.: Neuromuscular blocking agents *in* Goodman, L. S., and Gilman, A.: The Pharmacologic Basis of Therapeutics, ed. 3, The Macmillan Company, New York, 1965, pp. 596-613.
28. Burns, J. J., and Conney, A. H.: Enzyme stimulation and inhibition in the metabolism of drugs, Proc. Roy. Soc. Med., 58:955-960, Nov. 1965.
29. van Dam, E. E., Overkamp, M., and Haanen, C.: The interaction of drugs, Lancet, 2:1027, 5 Nov. 1966.
30. Cullen, S. I., and Catalano, P. M.: Griseofulvin-Warfarin antagonism, JAMA, 199:582-583, 20 Feb. 1967.
31. Cucinell, S. A., Conney, A. H., Sansur, M., and Burns, J. J.: Drug interactions in man. I. Lowering effect of phenobarbital on plasma levels of bishydroxycoumarin (Dicumarol®) and diphenylhydantoin (Dilantin®), Clin. Pharm. Ther., 6:420-429, July-Aug. 1965.

32. Cucinell, S. A., Odessky, L.: Weiss, M., and Dayton, P. G.: The effect of chloral hydrate on bishydroxycoumarin metabolism. A fatal outcome, JAMA, 197:366-368, 1 Aug. 1966.

33. Fox, S. L.: Potentiation of anticoagulants caused by pyrazole compounds, JAMA, 188:320-321, 20 Apr. 1964.

34. Elias, R. A.: Effect of various drugs on anticoagulant dosage *in* Nichol, E. S., Chairman, Editorial Board: Anticoagulant Therapy in Ischemic Heart Disease, Grune and Stratton, New York, 1965, p. 443.

35. Elion, G. B., Callahan, S., Nathan, H., Bieber, S., Rundles, R. W., and Hitchings, G. H.: Potentiation by inhibition of drug degradation: 6-substituted purines and xanthine oxidase, Biochem. Pharmacol., 12:85-93, Jan. 1963.

36. DeConti, R. C., and Calabrisi, P.: Use of allopurinol for prevention and control of hyperuricemia in patients with neoplastic disease, New Eng. J. Med., 274:481-486, 3 Mar. 1966.

37. Kristensen, M., and Hansen, J. M.: Potentiation of the tolbutamide effect by Dicumarol, Diabetes, 16:211-214, April 1967.

38. Hansen, J. M., Kristensen, M., Skovsted, L., and Christensen, L. K.: Dicumarol-induced diphenylhydantoin intoxication, Lancet, 2:265-226, 30 July 1966.

39. Horwitz, D., Lovenberg, W., Engelman, K., and Sjoerdsma, A.: Monamine oxidase inhibitors, tyramine, and cheese, JAMA, 188:1108-1110, 29 June 1964.

40. Sjoqvist, F.: Psychotropic drugs (2) Interaction between monamine oxidase (MAO) inhibitors and other substances, Proc. Roy. Soc. Med., 58:967-978, Nov. 1965.

41. Waddell, W. J., and Butler, T. C.: The distribution and excretion of phenobarbital, J. Clin. Invest., 36:1217-1226, Aug. 1957.

42. Payne, J. P., and Rowe, G. G.: The effects of mecamylamine in the cat as modified by the administration of carbon dioxide, Brit. J. Pharmacol., 12:457-460, Dec. 1957.

43. Milne, M. D.: Influence of acid-base balance on efficacy and toxicity of drugs, Proc. Roy. Soc. Med., 58:961-963, Nov. 1965.

44. Field, J. B., Ohta, M., Boyle, C., and Remer, A.: A potentiation of acetohexamide hypoglycemia by phenylbutazone, New Eng. J. Med., 277:889-894, 26 Oct. 1967.

45. Inglis, J. M., and Barrow, M. E. H.: Premedication, a reassessment, Proc. Roy. Soc. Med., 58:29-32, Jan. 1965.

46. Barsa, J., and Saunders, J. C.: A comparative study of tranylcypromine and pargyline, Psychopharmacologia, 6:295-298, 14 Oct. 1964.

47. Shoonmaker, F. W., Osteen, R. T., and Greenfield, J. C., Jr.: Thioridazine (Mellaril®)-induced ventricular tachycardia controlled with an artificial pacemaker, Ann. Int. Med., 65:1076-1078, Nov. 1966.

48. Selzer, A., and Wray, H. W.: Quinidine Syncope. Paroxysmal ventricular fibrillation occurring during treatment of chronic atrial arrhythmias, Circulation, 30:17-26, July 1964.

49. Jarvik, M. E.: Drugs used in the treatment of psychiatric disorders *in* Goodman, L. S. and Gilman, A.: The Pharmacologic Basis of Therapeutics, ed. 3, The Macmillan Company, New York, 1965, pp. 159-214.

50. Ibid.

51. Weiner, M.: Effect of centrally acting drugs on the action of coumarin anticoagulants, Nature, 212:1599-1600, 31 Dec. 1966.

52. Roberts, J., Ito, R., Reilly, J., and Cairoli, V. J.: Influence of reserpine and beta TM 10 on digitalis induced ventricular arrhythmia, Circ. Res., 13:149-158, Aug. 1963.

53. Dollery, C. T.: Physiological and pharmacological interactions of antihypertensive drugs, Proc. Roy. Soc. Med., 58:983-987, Nov. 1965.

54. Abramson, E. A., Arky, R. A., and Woeber, K. A.: Effects of propranolol on the hormonal and metabolic response to insulin-induced hypoglycemia, Lancet, 2:1386-1388, 24 Dec. 1966.

55. Lowenthal, I., and Fisher, L. M.: The effect of thyroid function in the prothrombin time response to warfarin in rats, Experientia (Basel), 13:253-254, 15 June 1957.

56. Doherty, J. E., and Perkins, W. H.: Digoxin metabolism in hypo- and hyperthyroidism, studies with tritiated digoxin in thyroid disease, Ann. Int. Med., 64:489-507, March 1966.

57. Schrogie, J. J., and Solomon, H. M.: The anticoagulant response to bishydroxycoumarin. II. The effect of D-thyroxin, clofibrate, and norethandrolone, Clin. Pharmacol. Ther., 8:70-77, Jan.-Feb. 1967.

58. Jawetz, E.: The use of combinations of antimicrobial drugs, Ann. Rev. Pharmacol., 8:151-170, 1968.

59. Symposium Number 7: Clinical effects of interactions between drugs. Chairman: The Rt. Hon. Lord Cohen of Birkenhead, Proc. Roy. Soc. Med., 58:943-999, Nov. 1965.

60. McIver, A. K.: Drug interactions, Pharm. J., 199:205-210, 2 Sept. 1967.

61. Gillette, J. R.: Theoretical aspects of drug interactions *in* Siegler, P. E. and Moyer, J. H., III: Animal and Clinical Pharmacological Techniques in Drug Evaluation, Year Book Medical Publishers, Chicago, 1967, pp. 48-66.

ATYPICAL CELLS IN G.I. ULCERATIVE DISEASE

"Considering our present knowledge of cells, cytologic examination is not specific for the diagnosis of ulcerative disease of the gastrointestinal tract. The results may be suggestive; and atypical cells may disappear in some instances when the patient improves (this is particularly true with chronic ulcerative colitis). These findings seem to make the technique of limited practical value. However, a knowledge of the atypical cells which may be seen in ulcerative diseases of the gastrointestinal tract is of more value to the cytologist in the careful cytologic examination for the presence of carcinoma. An appreciation of the possible significance of these cells may prevent the making of a false-positive cytodiagnosis."

—NELSON D. HOLMQUIST, M.D., New Orleans
Audio-Digest Internal Medicine, Vol. 15, No. 18